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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/619,059	07/18/00	DEYOUNG L	GENENT.047C1

EXAMINER	
ALLEN, M	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 10/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/619,059	Applicant(s) DEYOUNG ET AL.	
	Examiner Marianne Allen	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claim 1 has been cancelled. Claims 2-21 have been newly introduced.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-10, 12-15, and 17-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,090,781. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to overlapping compositions containing NGF.

Claim Rejections - 35 USC § 112

Claims 2-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "pharmaceutically effective amount of nerve growth factor." However, the claim fails to indicate the condition that this amount is effective for. In the absence of such a condition, the metes and bounds of the amount of NGF encompassed by the claims cannot be determined.

The recitation "at least about" in claim 13 is ambiguous in that the metes and bounds intended are not clear.

Claim 10 lacks antecedent basis in claim 2 for the inclusion of benzyl alcohol in the composition. Likewise, the additional components in claims 15 and 16 lack antecedent basis in claim 2.

Claim 10 contains a typographical error, "form."

Claims 13-14 recite the limitation "said acetate ion" in the second line of both claims. Claim 2 does not refer to acetate ions.

Claims 6, 15, and 16 recite "NGF." Claim 2 does not use this acronym. It appears that claim 2 should be amended to refer to "nerve growth factor (NGF)" for clarity.

Claim 21 recites "wherein the nerve growth factor is secreted from Chinese hamster ovary cells." It is unclear whether the composition contains CHO cells themselves or NGF that has been produced from CHO cells and purified.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4, 12, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Calbiochem 1994/1995 product catalog.

The Calbiochem 1994/1995 product catalog indicates that murine nerve growth factor was commercially available. According to company representatives, this catalog would have been available to the public in early 1994. The NGF product was lyophilized from a sodium acetate and sodium chloride solution. The reference is silent as to the concentration of the sodium acetate and sodium chloride and the pH of the solution prior to lyophilization. Absent evidence to the contrary, the amount of NGF in the vial would be pharmaceutically effective.

Claims 2, 4-5, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Apfel et al. (Annals of Neurology, 29(1): 87-90, January 1991).

Apfel et al. teaches administering murine NGF in a 0.05 M sodium acetate buffer. (See page 87, right column.) The reference is silent as to the volume, concentration, and amount of NGF administered. However, the amount was clearly pharmaceutically effective. (See abstract.)

Claims 2-6, 11-14, 17-18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Della Valle et al. (U.S. Patent No. 5,210, 185).

Della Valle et al. teaches a method for the purification of human NGF, as well as NGF compositions and kits. (See column 6, step 8, lines 14-20). The mature protein is a 118 amino acid dimer. (See column 3, lines 41-45.) With respect to claim 20, the limitation "rhNGF" (abbreviating recombinant human nerve growth factor) is deemed to be a process limitation which is given no patentable weight in a composition claim except insofar as it further defines the structure of the product. The NGF of della Valle et al. would possess the same structure as that recombinantly produced absent evidence to the contrary. NGF was stored in aliquots at -80 degrees Celsius in 0.05 M sodium acetate buffer (i.e., 50 mM that is between 0.1 to 200 mM, as it relates to claims 2, 4-5, 13-14, and18) at pH 5.0 (i.e., pH 5 to 6; as it relates to claim 3) with 0.1 M NaCl. In that 0.1 M NaCl encompasses a physiologically acceptable concentration of NaCl, della Valle anticipates claim 12. The NGF concentration disclosed by Della Valle is between 0.01% and 1% (i.e., 0.1 mg/ml to 10 mg/ml, columns 7-8; as it relates to between 0.07 to 20 mg/ml in claims 6 and 13-14). Physiologically acceptable surfactants disclosed in della Valle's pharmaceutical compositions containing NGF include Tween 61 (see Table 4; as it relates to claim 11).

Claims 2-3, 5-6, 11-14, and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Knepp et al. (WO 95/058845).

Knepp et al. discloses and claims pharmaceutical compositions of NGF comprising NGF, biologically acceptable salts, a buffer to maintain the pH between about 4.5-6.0, and water. (See abstract and claims.) Claim 4 is particularly directed to the pH range 5.0 to about 5.4. Use of surfactants is disclosed. (See page 4, line 39.) A preferred form of NGF is recombinant human

NGF that may be produced from Chinese hamster ovary cells. (See page 5, lines 6-18.) The preferred salt is sodium chloride. (See page 6, lines 6-7.) A suitable buffer is acetic acid/acetate. (See page 6, line 24.) Compositions containing therapeutically effective amounts of NGF are disclosed. (See page 10, lines 2-7 and claims 3 and 13.) The ranges of the various components disclosed overlap those of the claims. The reference indicates that buffers other than acetate are preferred if the formulation is going to be lyophilized; however, Knepp's invention is clearly directed to the stability of NGF in aqueous form. As such, acetate would have been considered a suitable (and preferred buffer) for an aqueous formulation by those of skill in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over della Valle et al. in view of Remington.

Della Valle et al. is as set forth above and further discloses that 16 mg of NaCl are to be included in a final volume of 2 mls in a kit containing NGF that results in a 138 mM solution of NaCl by definition (see column 8), which is considered to be a *de minimis* variation in NaCl concentration that is obviously within an acceptable range of 136 mM or 142 mM. The pH of 5.5 is considered to be a *de minimis* variation in pH from pH 5.0 and within an obvious acceptable range of pH 5.0. Moreover, step 6 of the NGF purification discloses sodium acetate buffer, pH 5.5 (column 5, line 66), thereby meeting this claim limitation. The difference in 50 mM versus 20 mM or 10 mM acetate buffer is considered to be a *de minimis* variation in acetate concentration that does not effect the pH of the buffer, and an obvious acceptable range for acetate buffer concentrations of 50 mM. However, della Valle do not specifically disclose use of preservatives well known within the art, such as benzyl alcohol.

Remington discloses acceptable preservatives used within the art. In particular benzyl alcohol is identified as a preservative on page 1286, in which 1 g of benzyl alcohol dissolves in about 30 mls. water (i.e., 3% maximum possible solution, see pg. 1056). Addition of 0.9% of benzyl alcohol as a preservative is a *de minimis* variation of 3%, and therefore does not distinguish the instant claims. However, Remington does not disclose NGF formulations.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add 0.9% benzyl alcohol to the della Valle's NGF formulation as a preservative, because each time a pharmaceutical dosage form is prepared, it is necessary to include a preservative in the formulation (see Remington, pg. 1449, 2nd column, 2nd paragraph).

Each of the specific limitations is deemed to be an obvious variant that would be arrived at by routine optimization of elements known to be useful in pharmaceutical compositions.

Claims 18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over della Valle et al. (U.S. Patent No. 5,210,185) in view of Heinrich (U.S. Patent No. 5,082,774) and della Valle et al. (U.S. Patent No. 5,457,034).

Della Valle et al. ('185) is applied as above. The reference does not disclose production of NGF in CHO cells.

Della Valle et al. ('034) and Heinrich each disclose production of the 118 amino acid form of NGF in CHO cells and purification thereof. (See abstract and claims of each.)

It would have been obvious to use the recombinantly produced NGF in the pharmaceutical compositions of della Valle et al. ('185). Della Valle et al. ('034) and Heinrich each provide the method of producing NGF in CHO cells and della Valle et al. ('185) discloses that recombinant forms have advantages in pharmaceutical preparations and have the same biological properties. (See column 3, lines 10-15 and column 4, lines 32-37.)

Claims 2-14 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knepp et al. (WO 95/058845) in view of della Valle et al. (U.S. Patent No. 5,210,185), Heinrich (U.S. Patent No. 5,082,774), Remington, Schmelzer et al. (Journal of Neurochemistry, 1992), and O'Connor et al. (U.S. Patent No. 5,763,394).

Knepp et al. is applied as above. The reference does not specifically disclose sodium acetate, benzyl alcohol as a preservative, or particular forms of NGF (e.g. 118 amino acid form).

Della Valle et al. is applied as above.

Remington is applied as above.

O'Connor et al. is relied upon to demonstrate that storage of aqueous pharmaceutical compositions of proteins at 2-8 degrees Celsius and use of 0.7-1% w/v benzyl alcohol as a preservative would have been routine in the art. (See column 2, lines 20-40; column 3, lines 50-55; column 4, lines 10-20; column 6, lines 10-15.) These parameters are not particular to the human growth hormone formulations disclosed.

Heinrich discloses production of the 118 amino acid form of NGF in CHO cells and purification thereof as set forth above. (See abstract and claims.)

Schmelzer et al. discloses production of a 120 amino acid form of human NGF in Chinese hamster ovary cells. Limited enzymatic digests produced a 118 amino acid form. (See abstract.)

It would have been obvious to take the aqueous formulations of NGF taught by Knepp et al. and add a preservative such as benzyl alcohol and store it in a 2 ml light-reducing vial as taught by Remington for their known advantages. It would have been obvious to use sodium acetate as the acetate buffer as taught by Della Valle et al. It would have obvious to use the 118 amino acid form of NGF produced in CHO cells as the form of NGF as taught by Heinrich or Schmelzer as Knepp et al. indicates that any form of NGF is intended to be suitable for the disclosed pharmaceutical compositions. O'Connor et al. demonstrate that the claimed preservative concentrations were routinely used by those of skill in the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 703-308-0666. The examiner can normally be reached on Monday-Friday, 9:00 am - 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703-308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Marianne P. Allen
Primary Examiner
Art Unit 1631

mpa
September 27, 2001